

Do Singapore Patients Require Lower Doses of Statins? The SGH Lipid Clinic Experience

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ABSTRACT

A substantial number of physicians in Asian countries believe that Asian patients need lower doses of statins to achieve therapeutic lipid target because of the smaller size of patients. This belief is deep rooted and we looked at the SGH Lipid Clinic to determine if our experience bears out this belief.

Between 1996 and August 2000, the Lipid Unit treated a total of 841 patients, of which 548 patients (77.5% Chinese, 12.1% Malays, 7.6% Asian Indians; 49.6% males, 50.4% females; 54.7% diabetics, 45.3% non-diabetic) were on statins alone. These patients had ≥ 2 coronary risk factors, diabetes mellitus or documented coronary heart disease. The pre-treatment lipid levels or the worst lipid levels available were entered as the baseline lipid values (mean LDL-C: 5.38+1.5 mmol/l). Duration of therapy ranged from six months to five years. The choice and titration of statins were determined by attending physicians.

The median statin dose (Simvastatin equivalent) was 20.0 mg with 52.5% requiring 20 mg or more. Statin dose did not differ between diabetic and non-diabetic subjects. The median statin dose was 15 mg for the lower two tertiles and 20 mg for the upper tertile; this difference did not achieve statistical significance. The reduction in LDL cholesterol was 41.5% (40.1-42.8) and total cholesterol was 33.0% (32.9-34.1). Only 25% of our patients achieved LDL cholesterol of less than 2.6 mmol/l whilst 77.5% had LDL cholesterol less than 3.4 mmol/l. Our experience at the Lipid Clinic suggests that the Asian patients require similar statin doses to achieve target cholesterol levels.

Keywords: asian patients, statins, LDL cholesterol, Body mass index, diabetes mellitus

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INTRODUCTION

Large mega-trials have shown unequivocally the benefits of statins (three hydroxy-3 methylglutaryl coenzyme A reductase inhibitor) in lowering cholesterol levels and coronary events in primary and secondary prevention⁽¹⁾. Knowledge about the need to treat high-risk individuals and clinical practice do not necessarily concur and this treatment gap occurs both in hospital⁽²⁾ and primary care practice⁽³⁾. This problem is compounded in Asian countries where many physicians believe that a lower statin dose is required to achieve target LDL cholesterol (LDL-C) given the lower body mass index (BMI) in our patients. This belief is unsubstantiated. Consequently, patients may be inadequately treated because dosages are not titrated appropriately. Data from trials on statins indicate that the western population need 20 mg to 40 mg of simvastatin^(4,5) and that reduction of LDL-C was of the magnitude of 30% to 35%. There is a paucity of data on response to statins in Asians, with only three published trials to date. The first trial using a titrate to goal protocol (STATT trial) used 20 mg to 80 mg of simvastatin⁽⁶⁾, and the second compared atorvastatin 10 mg to 20 mg versus simvastatin 10 mg to 20 mg⁽⁷⁾. The STATT trial demonstrated a LDL-C reduction of 45.4% but the mean statin dose was 27.5 mg. At doses of 20 mg simvastatin, only 72.2% reached target LDL-C whilst the rest required upward titration of dosages to achieve LDL-C goals. A third trial in Japanese subjects used 5 mg of simvastatin⁽⁸⁾ with LDL-C reduction of 27.7%. However, there are no published data to suggest that response to statins is dependent on BMI or weight, or that Asians may require lower doses of statins. We looked at the response to statin therapy in patients being treated for high risk dyslipidaemia to determine the statin dose and magnitude of cholesterol and LDL-C reduction in a non trial, clinical setting.

METHODS

Between 1996 and August 2000, the Lipid Unit treated a total of 841 patients for various lipid problems.

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Table I. Changes in Lipid Parameters with Statin therapy.

Groups	% decrease in Chol (95%CI)	% decrease in TG (95%CI)	% increase in HDL-C (95%CI)	% decrease in LDL-C * (95%CI)	Median statin dose(mg)
*BMI<23.8(kg/m ²) (N=165)	33.9 (31.9-35.8)	15.8 (8.9-22.7)	3.5 (-1.1-8.1)	42.0 (39.6-44.4) (N=142)	15
*23.8≤BMI<26.8 (kg/m ²) (N=174)	32.8 (30.9-34.7)	16.0 (9.2-22.9)	5.8 (1.3-10.3)	42.5 (40.2-44.9) (N=148)	15
*BMI≤26.8 (kg/m ²) (N=173)	32.6 (30.7-34.4)	21.0 (14.3-27.6)	4.0 (-0.4-8.6)	40.0 (37.6-42.3) (N=150)	20
DM (N=300)	32.4 (31.0-33.8)	18.1 (13.0-23.3)	3.5 (0.1-6.8)	40.1 (38.3-42.0) (N=249)	20
Non DM (N=248)	33.7 (32.1-35.2)	17.7 (12.2-23.2)	5.1 (1.4-8.7)	42.8 (40.8-44.8) (N=222)	20
All Groups (N=548)	33.0 (31.9-34.1)	17.9 (14.1-21.7)	4.3 (1.8-6.8)	41.5 (40.1-42.8) (N=471)	20

Each BMI group was equivalent to a tertile of the whole group. Differences between groups were taken to be significant when $p < 0.05$. Differences in statin dosages using Kruskal-Wallis test were not significant between BMI groups or between DM and non DM patients. Differences in lipid parameters between groups were derived by analysis of variance and were all not significant. Total number of subjects was 548 and excluded those with familial hypercholesterolaemia (clinical criteria and/or genetic analysis). The conversion⁽¹⁰⁾ to Simvastatin equivalent was as follows: Simvastatin 10 mg = Atorvastatin 5 mg = Cerivastatin 0.3 mg = Fluvastatin 40 mg = Pravastatin 20 mg. CI: Confidence Interval; BMI: body mass index; Chol: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; DM: diabetes mellitus. *LDL-C was not available when TG was >4.5 mmol/l. *BMI was not available in some subjects when height was not captured.

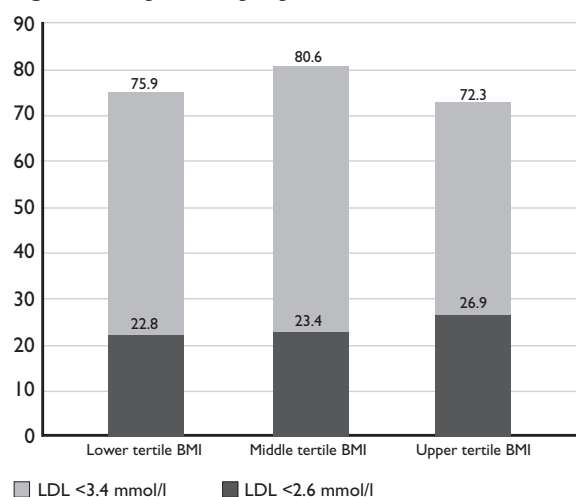
A total of 548 patients (or 65%) were on statins alone, consisting of 77.5% Chinese, 12.1% Malays, 7.6% Asian Indians; 49.6% males, 50.4% females; 54.7% diabetics and 45.3% non diabetic. Referrals came from routine health screening, primary care physicians, self-referrals, cardiologists, neurologists and gastroenterologists. Patient characteristics and ethnic composition were representative of the general population⁽⁹⁾. Reasons for referrals included those with high coronary risk (≥ 2 risk factors), diabetes mellitus or secondary prevention (i.e. established coronary artery disease such as coronary bypass grafting, angioplasty, myocardial infarction or ischaemic heart disease). Patients whose LDL-C remained elevated after a period of dietary change, were treated with statins. The pre-treatment lipid levels or the worst lipid levels available were entered as the baseline lipid values. Duration of therapy ranged from six months to five years. The choice (Atorvastatin, Cerivastatin, Fluvastatin, Pravastatin or Simvastatin) and titration of statins were determined by attending physicians. The dosages of each statin were converted to Simvastatin equivalent⁽¹⁰⁾ (5 mg Atorvastatin = 10 mg Simvastatin = 20 mg Pravastatin = 40 mg Fluvastatin = 0.3 mg Cerivastatin) as it was the first statin available for use in our practice. The post-treatment lipid levels

were taken as the best profile after at least six months of statin therapy.

In accordance with the Ministry of Health clinical practice guidelines for lipids⁽¹¹⁾, high risk patients were identified as those with established coronary artery disease, diabetes mellitus or two or ≥ 2 of the following risk factors:

- 1) age ≥ 45 in males and ≥ 55 in females
- 2) current smokers
- 3) family history of premature atherosclerosis in male first degree relatives under 55 years and females under 65 years
- 4) hypertension (BP $\geq 140/90$ mmHg or on anti-hypertensive treatment) and
- 5) low HDL cholesterol (HDL-C) (<1.0 mmol/l).

Total cholesterol, triglyceride and HDL-C (after separation from LDL and VLDL by dextran sulphate and magnesium chloride) were measured by enzymatic methods using Kodak Ektachem clinical chemistry slides. LDL-C was calculated by Friedewald's formula when triglyceride was less than 4.5 mmol/l. The number of subjects with LDL-C available for analysis was 471. Height (to the nearest millimetre) was recorded in all subjects without shoes, and weight (in kilograms) was measured in subjects in light clothing using electronic

Fig. 1 Percentage achieving Target LDL-C.

The figure shows the percentage of patients achieving LDL targets of less than 3.4 mmol/l and 2.6 mmol/l for each tertile of body mass index. Differences in percentages between groups were analysed by Mantel-Haenszel test with $p < 0.05$ as being significant. There was no difference between the patients in each tertile of body mass index.

weighing scales (Seca model 220). Diagnosis of diabetes mellitus was based on the 1985 World Health Organisation diagnostic classification criteria⁽¹²⁾. LDL-C goal for primary prevention was defined as LDL-C < 3.4 mmol/l and secondary prevention as LDL-C goal < 2.6 mmol/l⁽¹¹⁾.

STATISTICS

Statistical analysis was performed using SPSS for windows version 9.01 (Chicago, IL). Differences in lipid parameters between BMI groups were derived by analysis of variance and taken to be significant when $p < 0.05$. Statin dosage in each tertile of BMI and between diabetics and non-diabetics was compared using the Kruskal-Wallis test. The differences in lipid parameters between diabetics and non-diabetics were compared using unpaired student's t-testing. Triglyceride was normalised by log-transformation before t-testing. Other lipid parameters approximated a normal distribution. Comparisons of the proportions of each tertile of BMI reaching primary and secondary prevention targets were analysed by Mantel-Haenszel test with $p < 0.05$ as being significant. Comparisons between ethnic groups were not done as the numbers were too small to allow for appropriate comparison between Chinese, Malays and Indians.

RESULTS

After treatment with a statin for at least six months duration, a 33.0% reduction in total cholesterol and 41.5% reduction in LDL-C was achieved. There was also a 17.9% reduction in triglyceride and 4.2%

elevation in HDL cholesterol (Table I). The magnitude of total cholesterol, LDL-C and triglyceride reduction and HDL-C elevation with statins did not differ between diabetics and non-diabetics. Similarly, the change in lipid profile with statin therapy across all tertiles of BMI was similar. The median statin dose (Simvastatin equivalent) in our patients was 20.0 mg with 52.5% requiring 20 mg or more. Although those in the highest tertile of BMI required a median statin dose of 20 mg whilst the lower two tertiles required a median statin dose of 15 mg, this difference did not reach statistical significance ($p = 0.052$) (Table I). The mean statin dose from the lowest to the highest tertile of BMI was 20.8 mg, 23.1 mg and 23.6 mg respectively. Again, the difference in mean statin dose did not reach statistical significance. Both diabetic and non-diabetic subjects required a median statin dose of 20 mg ($p = 0.26$). 77.5% of our patients had LDL-C less than 3.4 mmol/l and 25% achieved LDL-C of less than 2.6 mmol/l. The proportion of subjects in each tertile of BMI achieving LDL-C targets of 2.6 mmol/l and 3.4 mmol/l did not differ when stratified by BMI using Mantel-Haenszel test (Fig. 1).

Two (0.4%) patients developed elevated creatinine kinase (CK) of greater than 10 fold, 1.4% had greater than three times elevation of alanine transaminase (ALT) and 0.4% had greater than three times elevation of aspartate transaminase (AST).

DISCUSSION

The magnitude of reduction in LDL-C and total cholesterol with statin therapy in our patients was comparable with that seen in non Asian populations in the 4S⁽⁴⁾, CARE⁽¹³⁾ and WOSCOPS⁽¹⁴⁾ studies. It was also consistent with two published studies on statin therapy in Asians^(6,7). This would suggest that Asian patients did not differ in their response to statin therapy. One other study in the Japanese population suggested that low dose simvastatin at 5 mg was sufficient for moderate hypercholesterolaemia⁽⁸⁾. However, that study was done in subjects without coronary heart disease, where the investigators achieved an LDL-C reduction of only 27.7% compared with the 41.5% reduction achieved in our subjects. Furthermore, the investigators achieved a mean LDL-C of 130.1 mg/dl (3.42 mmol/l) at the end of 12 months of therapy whilst more than three-quarters of our subjects had LDL-C below 3.4 mmol/l. This would suggest that even in the Japanese population, titration of statin doses upwards was needed if they were to achieve the same magnitude of LDL-C reduction seen in our population. The LDL-C reduction across all tertiles of BMI was similar at comparable statin doses. In addition, the proportions

of patients achieving primary or secondary prevention targets across all three tertiles of BMI did not differ, thereby dispelling the myth that a lower BMI in Asian patients necessitates a lower statin dose.

Furthermore, it was interesting to note that diabetics and non-diabetics also demonstrated similar magnitude of LDL-C and total cholesterol reduction. The present Adult Treatment Panel III guidelines⁽¹⁵⁾ and the Clinical Practice Guidelines (Lipid) in Singapore⁽¹¹⁾, advocate treating diabetics to a secondary prevention target. Implications of these guidelines suggest that aggressive use of statin at appropriate dosing is required to achieve LDL-C target in the diabetic population.

Treatment with statins was demonstrated to be safe and patients with elevation of creatinine kinase above ten fold was minimal (0.4%). Likewise, the occurrence of greater than three fold elevation of ALT was only 1.4% and ALT was 0.4%.

Although we had shown data that the mean statin dose across tertiles of BMI did not differ, we believe that the use of median statin dose was more appropriate as statins are usually prescribed in multiples of 5 or 10 mg. The median statin dose for our patients was 20 mg of simvastatin equivalent, with more than half requiring higher doses. This was comparable to the 63% in the 4S study requiring 20 mg of simvastatin. In the STATT trial⁽⁶⁾ which was conducted in Asian patients, 72.2% required 20 mg of simvastatin to reach LDL-C of less than 2.6 mmol/l whilst the remainder needed titration of simvastatin doses upwards to attain therapeutic LDL-C goals. Our lipid clinic experience showed that despite a median statin dose of 20 mg (simvastatin equivalent), only 77.5% achieved primary prevention target whilst a dismal 25% achieved secondary prevention target. Dosages of statins would probably need to be titrated beyond 20 mg (simvastatin equivalent) to achieve LDL-C goals. The magnitude of reduction in LDL-C and total cholesterol by statins did not appear to be influenced by Asian ethnicity or BMI.

CONCLUSION

Our experience at the Lipid Clinic suggests that statin dosages should be titrated upwards when target lipid levels are not achieved in both lean and obese Asian patients. Appropriate increase in statin doses should be dictated by adequacy of LDL-C reduction rather than by ethnicity.

LIMITATIONS

The conclusions drawn from this data are limited because it was a cross sectional data from a routine

lipid clinic and not a prospective series. However, its strength lies in the fact that this was the usual clinical setting where most clinicians practice and not in the artificial setting of a clinical trial. The clinic was run by trained lipidologists (all three authors) and one could argue that it was therefore not representative of usual general practice since they would be more aggressive in lipid lowering regime. The type of attending physician notwithstanding, only 25% achieved secondary prevention target. We are of the opinion that the median statin dose required to achieve desirable targets is likely to be higher than what was demonstrated in this series.

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